REMARKS/ ARGUMENTS

Applicant has carefully studied the non-final Examiner's Action mailed December 3, 2009, having a shortened statutory period for response set to expire on March 3, 2010. These explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance. Applicant responds to the outstanding Action by centered headings that correspond to the centered headings employed by Office, to ensure full response on the merits to each finding of Office.

Status of the Claims

Claims 1 through 26 were presented in the originally-filed application, and subjected to a restriction requirement mailed on March 30, 2007. Applicant elected to pursue claims 1 through 18, and withdrew the remaining claims as drawn to a non-elected invention. Claims 1 and 12 have been amended herein. Support for the revisions can be found in the originally filed application at pages 23-24, paragraph [079]; page 24, paragraph [081], and page 11, paragraph [033]. Claim 15 is cancelled and the subject matter incorporated into claim 12. Accordingly, claims 1, 5 through 12, 14 and 16 through 18 are still pending.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 5-12 and 14-18 stand rejected under 35 USC 103(a) as obvious in light of *Pittenger, et al.* (U.S. Pat. No. 6,387,369), *Dengler, et al.* (Herz, 2002 Nov;27(7):598-610.), *Edelberg, et al.* (P.G. Pub. 2003/0091547), *Isner, et al.* (U.S. Pat. No. 5,980,887), *Erices, et al.* (Br. J. Haematol. 2000, 109, 235-242), and *Lim, et al.* (Bone Marrow Transpl. 1999, 24, 965-970). The combination of *Pittenger, et al.*, *Dengler, et al.*, *Edelberg, et al.*, *Isner, et al.*, *Erices, et al.*, and *Lim, et al.* do not obviate the claimed invention because (1) the combined references do not teach the claimed invention; and (2) the combination inappropriately alters the principle operation of a reference; (3) a *prima facie* case has not been established.

Pittenger, et al., *Dengler, et al.*, *Edelberg, et al.*, *Isner, et al.*, *Erices, et al.*, and *Lim, et al.* cannot obviate the claimed invention because the references, as combined, do not teach the claimed invention. "All words in a claim must be considered in judging the patentability of that claim against the prior art."[1] In the rejection, it was stated that it would be obvious to replace

[1] MPEP 2143.03(citing *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

MSCs of *Pittenger, et al.* with UCBCs because *Dengler, et al.* provides stem cells in UCBCs possess the ability to differentiate into cardiac myocytes.[2]

The art has found that UCBC-derived stem/progenitor cells are distinct from stem/progenitor cells found in bone marrow and peripheral blood.[3] For example, *Nishiyama, et al.* shows that compositions of UCBCs do not possess endothelial progenitor cells or MSCs, but can be differentiated in culture to generate UCB-based MSCs.[4] Applicant also notes that claim 1 provides for

> obtaining a composition comprising an umbilical cord blood cell, wherein the human umbilical cord blood cell has not been cultured;
> generating myocytes further comprising:
> administering an effective amount of the composition comprising an umbilical cord blood cell to an individual with a circulatory disorder, wherein the umbilical cord blood cell differentiates into a cardiac muscle cell after administration.

Claim 12 also provides for administering a composition of uncultured UCBC. The Office's findings provide that *Pittenger, et al.* disclose administering MSCs, and that the MSCs may be substituted because *Dengler, et al.* states that UCBCs comprise stem cells that can differentiate into cardiac myocytes, and *Edelberg, et al.* and *Isner, et al.* disclose that endothelial progenitor cells are found in UCB.[5] The Office also found that *Dengler, et al.* provides that different cell sources may be used to generate cardiomyocytes, thereby providing a reason why one of skill in the art would modify *Pittenger, et al.* to include UCBC of *Dengler et al.*[6] *Dengler, et al.* state "[u]mbilical cord stem cells at the present time show few differences compared with embryonic stem cells regarding the use for cardiac regeneration[,]"[7] but notes that "human embryonic stem cells have a very low efficiency of conversion into cardiomyocytes."[8] As noted above, the UCB-based stem/progenitor cells differ from bone marrow and peripheral blood, such as the MSCs of *Pittenger, et al.* Further, claims 1 and 12 provide for

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[2] Page 3 of the non-final Office Action, dated December 3, 2009.
[3] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2017, column 2 to page 2018, column 1.
[4] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2020, column 1.
[5] Page 3 of the non-final Office Action, dated December 3, 2009.
[6] Page 7 of the non-final Office Action, dated December 3, 2009.
[7] Dengler,, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 604, column 2.
[8] Dengler,, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 603, column 2.

obtaining a composition comprising an umbilical cord blood cell, wherein the human umbilical cord blood cell has not been cultured[.]

However, Applicant respectfully points out that *Pittenger, et al.* used cultured cells,[9] and specifically provided a detailed disclosure on culturing with fusigens and other cell culturing techniques.[10] Likewise, *Edelberg, et al.* culture EPCs in PDGF prior to administration.[11] In all the examples presented in *Edelberg, et al.*, bone marrow endothelial precursor cells were cultured in DMEM with 10% FCS,[12] or bone marrow cells were isolated and grown in DMEM with 10% FCS.[13] Lim also cultured the UCBC for hematopoietic progenitor cells, by growing the cells in IMDM with cytokines.[14] As can be seen, the cited references that undertook primary research used cultures of cells, and did not administer the cells directly.

However, Applicant respectfully points out that culturing of cells for growth or to artificially differentiate the cells, alters the cell composition from uncultured cells,[15] such as genetic alteration in culture.[16] Furthermore, in a previous study by *Nishiyama, et al.*, they used cells after immediately thawing cryopreserved UCBCs, which failed to transdifferentiate into cardiomyocytes.[17] *Urbich, et al.* also noted that freshly isolated bone marrow or blood derived mononuclear cells poorly augmented neovascularization, even though the cells efficiently augment vascularization when cultured.[18] Applicant points out that FCS may cause cultured cells to have some xenografts issues, due to the bovine supplement, that would need to be addressed before engraftment.

The Office also stated that

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[9] Pittenger, et al. (U.S. Pat. No. 6,387,396); column 2, lines 10-14.
[10] Pittenger, et al. (U.S. Pat. No. 6,387,396); column 3, lines 35-67.
[11] Edelberg, et al. (P.G. Pub. 2003/0091547); page 9, paragraphs [0120], [0121]; page 2, paragraph [0018].
[12] Edelberg, et al. (P.G. Pub. 2003/0091547); page 11, paragraph [0149].
[13] Edelberg, et al. (P.G. Pub. 2003/0091547); page 15, paragraph [0185].
[14] Lim, et al. The number of nucleated cells reflects the hematopoietic content of umbilical cord blood for transplantation. Bone Marrow Transplant. 1999 Nov;24(9):965-70; page 966, column 2.
[15] See, Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 344, column 2 ("[S]pecifc problem arises when cells are ex vivo expanded and cultured because the culture conditions (culture supplements such as FCS and cytokines, plastic) rapidly change the phenotype of the cells.").
[16] See, Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 2 (discussing problems with embryonic stem cells and noting genetic alterations in long-term cultures).
[17] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 1.
[18] Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 345, columns 1-2.

> [i]t is understood that claim 9 discloses that the injection is made directly to heart tissue, and this disclosure might be considered what applicant alleged that the invention requires administration of the cells into the infracted regions. However, it is clearly disclosed in claim 10 that the administration can be carried out systemically. Thus, the claimed method does not particularly require injection of the cells into the infarcted area.[19]

Applicant traverses the Office's findings and points out that claim 9 does specifically require that the cells be administered directly to heart tissue.

Furthermore, amended claim 12 provides "administering the composition comprising a human umbilical cord blood cell directly to the infarcted tissue or heart tissue adjacent to the infarcted tissue[.]" It is noted that *Pittenger, et al.* do not administer cells to infracted cardiac tissue.[20] *Dengler, et al.* stated that the present studies do not administer UCBC to infracted regions, and the art notes that current studies involving myocyte generation could result from fusion of the stem cells and live host cells.[21] "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious."[22] Implanting adult MSCs, i.e. bone marrow-derived MSCs, in infarct areas where scar tissue formed has resulted in the formation of more scar tissue.[23] However, the claimed invention provides for generating functioning myocytes,[24] as evidenced by the specification which monitored echocardiograms of the left ventricle,[25] left ventricular fractions,[26] and cardiac histology.[27] Applicant points out there are differences between culturing stem cells with active cardiomyocytes; and treating an infarcted area with dead cardiomyocytes and forming scar tissue. Applicant notes that none of the cited references tested the functionality of the cells. *Dengler, et al.*, states that more tests must be performed to "determine to what extent cellular

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[19] Page 6 of the non-final Office Action, dated December 3, 2009.
[20] See, Pittenger, et al. (U.S. Pat. No. 6,387,369), column 5, lines 45-50 (MSCs grafted into athymic rats).
[21] Dengler,, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2.
[22] MPEP 2141.02(I) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983)) (emphasis in original).
[23] Page 4, paragraph 10 of the Application (citing Wang, et al., 2000 J. Thorac. Cardiovasc. Surg. 120:999-1005).
[24] See, claim 1.
[25] Page 24, paragraph [082] of the Application.
[26] Page 24, paragraph [083] of the Application.
[27] Page 27, paragraph [091] to page 28, paragraph [093]; Figures 4(A) and (B) of the Application.

engraftment exerts an active effect (i.e., contributes to contractile activity) vs a passive effect (i.e., prevention of infarct expansion and/or remodeling) on cardiac function."[28] *Dengler, et al.*, stated that transdifferentiation undertaken in many of the studies was due to cell fusion, and that further studies must consider the ischemically damaged cardiac cells.[29] Contemporary studies that claimed to show myocyte generation could result from fusion of the stem cells and live host cells.[30] The cited references also provide "it is not yet clear *if* and how injected or infiltrating stem cells … electrically integrate into the surrounding myocardium[,]"[31] and this electrical integration is important, as "even small areas of imperfectly integrated tissues are likely to severely alter electrical conduction and syncytial contraction of the heart, with long-term life-threatening consequences."[32] The art also recognizes that studies must be undertaken to "assess responsiveness toward cardiomyogenic, endothelia, hepatic, neuronal, and pancreatic differentiation[,]"[33] indicating the art does not recognize the capacity for MSC to generate cardiomyocytes.

It is respectfully submitted that all claim limitations "must be considered in judging the patentability of that claim against the prior art[,]"[34] and that the invention cannot be distilled to the gist of the invention.[35] The combined references fail to disclose the use non-cultured UCBC and do not disclose generation of functional cardiomyocytes. Further, the references fail to disclose administering UCBC compositions directly to infracted tissue or adjacent tissue. Considering the claimed invention, as a whole, the combined references fail to disclose the invention, and therefore cannot obviate the claimed invention.

The combination of *Pittenger, et al.*, *Dengler, et al.*, *Edelberg, et al.*, *Isner, et al.*, *Erices, et al.*, and *Lim, et al.* also fail to obviate the invention as the proposed combination would

[28] Dengler, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 607, column 2 to page 608, column 1.
[29] See Dengler, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2.
[30] Dengler, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2.
[31] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2 (emphasis added).
[32] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 601 column 2.
[33] Kern, S. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May;24(5):1294-301. Epub 2006 Jan 12, page 1300, column 2.
[34] MPEP 2143.03 (citing *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970).
[35] MPEP 2141.02(II).

inappropriately alter the principle mode of operation of a reference. Where "the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, … the teachings of the references are not sufficient to render the claims *prima facie* obvious."[36] Claims 1 and 12 provide for

> obtaining a composition comprising an umbilical cord blood cell, wherein the human umbilical cord blood cell has not been cultured[.]

However, Applicant respectfully points out that *Pittenger, et al.* used cultured cells,[37] and specifically provided a detailed disclosure on culturing with fusigens and other cell culturing techniques.[38] Likewise, *Edelberg, et al.* culture EPCs in PDGF prior to administration.[39] In all the examples presented in *Edelberg, et al.*, bone marrow endothelial precursor cells were cultured in DMEM with 10% FCS,[40] or bone marrow cells were isolated and grown in DMEM with 10% FCS.[41] *Lim, et al.* also cultured the UCBC for hematopoietic progenitor cells, by growing the cells in IMDM with cytokines.[42] As can be seen, the cited references that undertook primary research used cultures of cells, and did not administer the cells directly.

However, Applicant respectfully points out that culturing of cells for growth or to artificially differentiate the cells, alters the cell composition from uncultured cells,[43] such as genetic alteration in culture.[44] Furthermore, in a previous study by *Nishiyama, et al.*, they used cells after immediately thawing cryopreserved UCBCs, which failed to transdifferentiate into

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[36] MPEP 2143.01 (VI) (citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)).
[37] Pittenger, et al. (U.S. Pat. No. 6,387,396); column 2, lines 10-14.
[38] Pittenger, et al. (U.S. Pat. No. 6,387,396); column 3, lines 35-67.
[39] Edelberg, et al. (P.G. Pub. 2003/0091547); page 9, paragraphs [0120], [0121]; page 2, paragraph [0018].
[40] Edelberg, et al. (P.G. Pub. 2003/0091547); page 11, paragraph [0149].
[41] Edelberg, et al. (P.G. Pub. 2003/0091547); page 15, paragraph [0185].
[42] Lim, et al. The number of nucleated cells reflects the hematopoietic content of umbilical cord blood for transplantation. Bone Marrow Transplant. 1999 Nov;24(9):965-70; page 966, column 2.
[43] See, Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 344, column 2 ("[S]pecifc problem arises when cells are ex vivo expanded and cultured because the culture conditions (culture supplements such as FCS and cytokines, plastic) rapidly change the phenotype of the cells."); Ito, et al. The AC133+CD38-, but not the rhodamine-low, phenotype tracks LTC-IC and SRC function in human cord blood ex vivo expansion cultures. Blood. 2010 Jan 14;115(2):257-60. Epub 2009 Nov 6, abstract; Sommer, et al. Excision of reprogramming transgenes improves the differentiation potential of iPS cells generated with a single excisable vector. Stem Cells. 2010 Jan;28(1):64-74, abstract; Parekh, et al. Differentiation of human umbilical cord blood-derived mononuclear cells to endocrine pancreatic lineage. Differentiation. 2009 Nov;78(4):232-40. Epub 2009 Aug 7, abstract.
[44] See, Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 2 (discussing problems with embryonic stem cells and noting genetic alterations in long-term cultures).

cardiomyocytes.[45] *Urbich, et al.* also noted that freshly isolated bone marrow or blood derived mononuclear cells poorly augmented neovascularization, even though the cells efficiently augment vascularization when cultured.[46]

Applicant submits that the use of culturing in *Pittenger, et al.*, *Edelberg, et al.*, and *Lim, et al.* change the physiology of the cells prior to administration, where the use of non-cultured cells does not. The obviousness finding requires that one find modify the references to not culture the cells of the cited references. However, by not culturing, and differentiating, the cells, the proposed change alters the principle manner in which the cells are administered.

Pittenger, et al., *Dengler, et al.*, *Edelberg, et al.*, *Isner, et al.*, *Erices, et al.*, and *Lim, et al.* cannot obviate the invention because a *prima facie* case of obviousness has not been established.

The Office's findings do not show that one of skill in the art would find the references, independently or combined, show that the administered cells of the cited references generate functional cardiomyocytes. The Office found that *Pittenger, et al.* discloses regenerating cardiac muscle and that *Dengler, et al.* and *Edelberg, et al.* discuss using UCBC which possess the ability to differentiate into cardiomyocytes.[47]

Applicant respectfully points out that *Pittenger, et al.* states it shows a "method for producing cardiomyocytes in vivo[,]"[48] which Applicant submits is not equivalent to regenerating cardiac muscle. Further, it is noted that none of the cited references tested the cells *in vivo* to confirm the cells integrate into the Purkinje network and/or contract. As noted above, and this electrical integration is important, as imperfectly integrated tissues will severely alter electrical conduction and syncytial contraction of the heart, with long-term life-threatening consequences.[49] "Once the findings of fact are articulated, Office personnel must provide an explanation to support an obviousness rejection under 35 U.S.C. 103."[50] However, *Nishiyama,*

[45] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 1.
[46] Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 345, columns 1-2.
[47] Page 3 of the non-final Office Action, dated December 3, 2009.
[48] See, Pittenger, et al. (U.S. Pat. No. 6,387,369), abstract.
[49] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 601 column 2.
[50] MPEP 2141(II).

et al. also noted studies of the myogenic potential, pointing out that the "papers failed to show clear evidence for cell fusion-independent cardiomyogenesis and efficiency of cardiomyogenic differentiation[,]"[51] and further found that the cardiomyogenic transdifferentiation efficiency was very high, whereas the frequency of nuclear fusions was very low.[52] The Office stated that "Dengler et al. clearly teach that umbilical cord blood cells containing stem cells can differentiate into cardiac myocytes." *Dengler, et al.* provides

> these human data should be interpreted as nothing more than a proof of principle for physiological repair mechanisms after myocardial infarction, because the functional relevance of these findings is still entirely unproven. In contrast to some animal data, especially the issues of true myocardial differentiation and the development of intercellular contacts for force transmission and electrical conductance have not been rigorously addressed in these studies."[53]

Further, *Dengler, et al.* stated that tests are required to "determine to what extent cellular engraftment exerts an active effect (i.e., contributes to contractile activity) vs a passive effect (i.e., prevention of infarct expansion and/or remodeling) on cardiac function[,]"[54] and that "it is not yet clear *if* and how injected or infiltrating stem cells … electrically integrate into the surrounding myocardium."[55] *Dengler, et al.* does not discuss using UCBC to generate functional cardiomyocytes, but that the art must perform further testing to determine if the cells integrate. Applicant respectfully submits that the findings do not explain why the methods described in the cited references would obviate claims drawn to generating functional cardiomyocytes.

Further, the claimed invention is drawn to uncultured cells, whereas the cited references disclose culturing and differentiating the cells before administration. Where the cited references differ from the claimed invention, "Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art."[56] Previous studies have found using cells after immediately thawing cryopreserved UCBCs

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[51] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 1.
[52] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2023, columns 1-2.
[53] Page 600, column 2
[54] Dengler, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 607, column 2 to page 608, column 1.
[55] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2 (emphasis added).
[56] MPEP 2141(III).

failed to transdifferentiate into cardiomyocytes,[57] or poorly augmented neovascularization, even though the cells efficiently augment vascularization when cultured.[58] Moreover, culturing of cells for growth or to artificially differentiate the cells, alters the cell composition from uncultured cells,[59] such as genetic alteration in culture.[60] Applicant therefore submits that the difference between the cited references and the claimed invention, such as the uncultured cells administered in the claimed invention, do not support a finding of obviousness.

Applicant submits that the combined references do not obviate the claimed inventions as the references do not teach the claimed invention. The art has found that UCBC-derived stem/progenitor cells are distinct from stem/progenitor cells found in bone marrow and peripheral blood, which were the subject matter of the cited references. The references also do not disclose administering a composition of uncultured UCBC. The references also do not administer UCBC to infracted regions of the heart or adjacent tissue, as provided for in claim 12. The art did not test to determine whether the formed myocytes were functioning myocytes. Additionally, the combination of references would inappropriately alter the principle mode of operation of a reference, as the cited references that undertook primary research used cultures of cells, and did not administer the cells directly. Culturing of cells for growth or to artificially differentiate the cells, alters the cell composition from uncultured cells, and the obviousness rejection therefore requires that one to modify the references to not culture the cells of the cited references which alters the principle manner in which the cells are administered. Finally, a *prima facie* case of obviousness has not been established. The cited references did not test the myocytes *in vivo* to confirm the cells integrate into the Purkinje network and/or contract.

[57] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 1.

[58] Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 345, columns 1-2.

[59] See, Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 344, column 2 ("[S]pecifc problem arises when cells are ex vivo expanded and cultured because the culture conditions (culture supplements such as FCS and cytokines, plastic) rapidly change the phenotype of the cells."); Ito, et al. The AC133+CD38-, but not the rhodamine-low, phenotype tracks LTC-IC and SRC function in human cord blood ex vivo expansion cultures. Blood. 2010 Jan 14;115(2):257-60. Epub 2009 Nov 6, abstract; Sommer, et al. Excision of reprogramming transgenes improves the differentiation potential of iPS cells generated with a single excisable vector. Stem Cells. 2010 Jan;28(1):64-74, abstract; Parekh, et al. Differentiation of human umbilical cord blood-derived mononuclear cells to endocrine pancreatic lineage. Differentiation. 2009 Nov;78(4):232-40. Epub 2009 Aug 7, abstract.

[60] See, Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 2 (discussing problems with embryonic stem cells and noting genetic alterations in long-term cultures).

However, electrical integration is important, as imperfectly integrated tissues will severely alter electrical conduction and syncytial contraction of the heart, with long-term life-threatening consequences. Further, the differences in using uncultured cells, as provided in the claimed invention, versus cultured cells of the cited references were not explained to show how/why the claimed invention would have been obvious.

Accordingly, Applicant respectfully requests the Office withdraw the 35 USC 103(a) rejection of claims 1, 5-12 and 14-18.

Provisional Double Patenting Rejection

Claims 1, 5-8, 10-12 and 15-17 are provisionally rejected for nonstatutory obviousness-type double patenting over claims 1-14 of U.S. Appl. No. 12/117, 197 and *Dengler, et al.* Applicant has submitted a terminal disclaimer thereby rendering this rejection moot. Accordingly, Applicant respectfully requests the Office withdraw the nonstatutory double patenting rejection of claims 1, 5-8, 10-12, and 15-17.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

/robert varkonyi/

By:_____

Robert Varkonyi
Reg. No. 63,885
180 Pine Avenue North
Oldsmar, Florida 34677
Attorney for Applicant

Dated: March 3, 2010
Customer No. 21,901

CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

I HEREBY CERTIFY that this correspondence is being electronically transmitted to the Patent and Trademark Office through EFS Web on March 3, 2010.

/lauren reeves/

Date: March 3, 2010

Lauren Reeves